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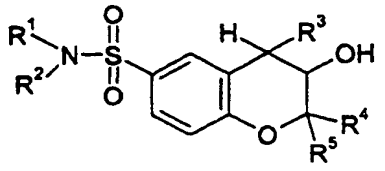
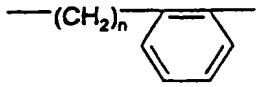
(54) Title: BENZOPYRANS HAVING POTASSIUM CHANNEL OPENING ACTIVITY



(I)



(II)

(57) Abstract

A compound of formula (I) where the indicated OH group in the 3– position is in the trans position with respect to R^3, and R^1 and R^2 are independently hydrogen or C_1 to C_5 alkyl, R^3 is a group of the formula: $-N(R^6)-COR^7$ where R^6 is hydrogen or C_1 to C_5 alkyl and R^7 is a C_6 to C_{10} monovalent aromatic group or a monovalent heteroaromatic group having a 5– or 6–membered heteroaromatic ring, or R^6 and R^7 together are 1,3–butadienylene or denote a group of formula $-(CH_2)_m-$ or formula (II) in which m is an integer of from 3 to 5 and n is 1 or 2, and R^4 and R^5 are, independently, C_1 to C_5 alkyl; or a N–oxide thereof; or a physiologically–hydrolysable and –acceptable ester of a compound of formula (I) or N–oxide thereof; or a physiologically acceptable acid addition or quaternary ammonium salt of a compound of formula (I), or of an ester or N–oxide thereof.

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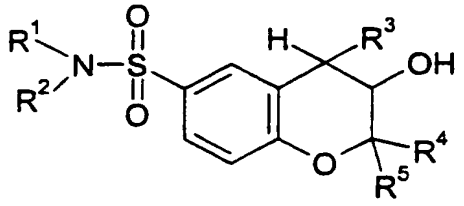
BENZOPYRANS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

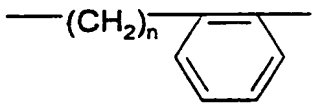
This invention relates to benzopyran derivatives, their preparation and their use as pharmaceuticals.

The invention provides, in one aspect, a compound of formula



I

where the indicated OH group in the 3- position is in the trans position with respect to R^3, and R^1 and R^2 are independently hydrogen or C_1 to C_5 alkyl, R^3 is a group of formula $-N(R^6)-COR^7$ where R^6 is hydrogen or C_1 to C_5 alkyl and R^7 is a C_6 to C_{10} monovalent aromatic group or a monovalent heteroaromatic group having a 5- or 6- membered heteraromatic ring, or R^6 and R^7 together are 1,3-butadienylene or denote a group of formula $-(CH_2)_m-$ or

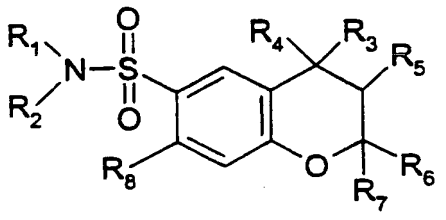


II

in which m is an integer of from 3 to 5 and n is 1 or 2, and R^4 and R^5 are, independently, C_1 to C_5 alkyl; or a N-oxide thereof; or a physiologically-hydrolysable and -acceptable ester of a compound of formula I or N-oxide thereof; or a physiologically acceptable acid addition or quaternary ammonium salt of a compound of formula I, or of an ester or N-oxide thereof.

It has been found that a compound of formula I where R^1 and R^2 are each hydrogen, R^4 and R^5 are each methyl and R^3 is a group of formula $-N(R^6)-COR^7$ where R^6 and R^7 together denote $-(CH_2)_4-$ is formed as a metabolite following administration to a subject of a compound of formula I of WO96/37490 in which R_1 is phenyl, R_2 is hydrogen, R_3 is a group of formula $-N(R_9)-COR_{10}$ in which R_9 and R_{10} together denote $-(CH_2)_4-$, R_4 is hydrogen, R_5 is hydroxy in the trans position with respect to R_3, R_6 and R_7 are each methyl and R_8 is hydrogen. Accordingly, the invention provides in another aspect a compound of formula I

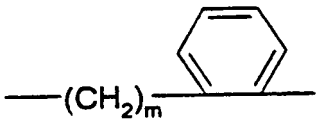
other than when present as a metabolite following administration to a subject of a compound of formula A :



A

wherein R_1 is phenyl, R_2 is hydrogen, R_3 is a group of formula $-N(R_9)-COR_{10}$ in which R_9 and R_{10} together denote $-(CH_2)_4-$, R_4 is hydrogen, R_5 is hydroxy in the trans position with respect to R_3, R_6 and R_7 are each methyl and R_8 is hydrogen.

In a further aspect, the invention relates to a compound of formula I other than when present as a metabolite following administration to a subject of a compound of formula A wherein R_1 is aryl, R_2 is H or C_{1-5}alkyl, or is C_{2-5}alkylene linked to R_1, R_3 is a group of formula $-N(R_9)-COR_{10}$ wherein R_9 is hydrogen and R_{10} is phenyl or pyridyl, or R_9 and R_{10} together are 1,3-butadienylene or represent a group of formula $-(CH_2)_n-$ or



in which n is an integer of from 3 to 5 inclusive and m is 1 or 2, R_4 is hydrogen and R_5 is hydroxy in the trans position with respect to R_3, R_6 and R_7 are independently C_1-C_5-alkyl, and R_8 is hydrogen or C_1-C_5-alkyl; or N-oxide thereof; or physiologically-hydrolysable and -acceptable ester of such a compound or N-oxide, or acid addition or quarternary ammonium salt of such a compound, N-oxide or ester.

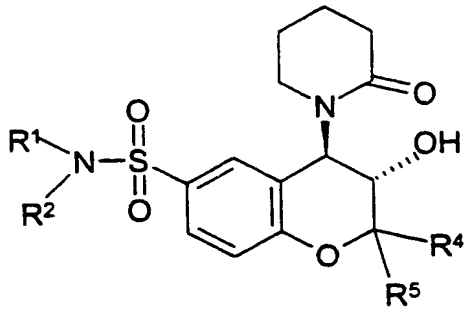
The invention relates preferably to compounds of formula I in isolated form.

Alkyl groups as R^1, R^2, R^4, R^5 and R^6 may be branched or straight chain. They may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, or pentyl such as n-pentyl, or 2,2-dimethylpropyl. R^1 and R^2 may be the same or different; preferably they are each hydrogen or each independently C_1 to C_5 alkyl, while in especially preferred compounds R^1 and R^2 are each hydrogen or R^1 is methyl and R^2 is 2,2-dimethylpropyl. R^4 and R^5 are both preferably methyl. R^6 in a group of formula $-N(R^6)-COR^7$ is preferably hydrogen or methyl, especially hydrogen.

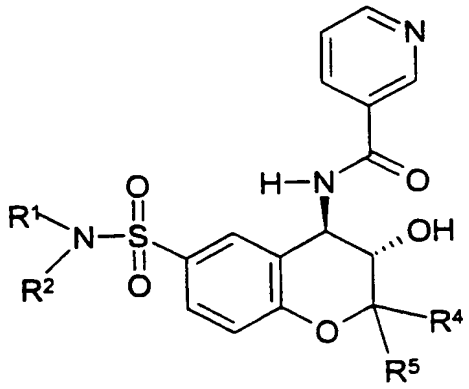
R^7 as an aromatic or heteroaromatic group is preferably phenyl, optionally substituted by 1 to 3 substituents selected from C_1-C_5 alkyl, such as methyl, C_1-C_5 alkoxy such as methoxy, halogen-substituted C_1-C_5 alkyl such as trifluoromethyl or halogen such as fluorine or chlorine, naphthyl or heteroaryl containing nitrogen in the ring such as pyridyl or pyrimidinyl.

In a preferred group of compounds of formula I, R^3 is a group of formula -N(R^6)-COR^7 in which R^6 is hydrogen and R^7 is pyridyl, especially 3-pyridyl, or R^6 and R^7 together are 1,3-butadienylene, trimethylene or tetramethylene, especially tetramethylene.

Especially preferred compounds are of formula IA or IB



IA



IB

where R^1, R^2, R^4 and R^5 are as hereinbefore defined.

More especially preferred are compounds of formula IA or IB in which R^1 and R^2 are each hydrogen, or R^1 is methyl and R^2 is 2,2-dimethylpropyl; and R^4 and R^5 are each methyl.

The invention, in so far as it relates to a compound of formula IA in which R^1 and R^2 are each hydrogen and R^4 and R^5 are each methyl, relates especially to that compound in isolated form, particularly as a product of a chemical synthesis.

Certain compounds of formula I form N-oxides, e.g. at the nitrogen atom of a pyridyl group. Such N-oxides have comparable activity and tolerability to the parent compounds and also form part of the invention.

The term "physiologically-hydrolysable and -acceptable ester" as used herein means an ester in which a hydroxy group (e.g. the indicated hydroxy group in formula I) is esterified and which is hydrolysable under physiological conditions to yield an acid which is itself physiologically tolerable at doses to be administered. As will be understood by those skilled in the art, such esters of pharmaceutically active parent compounds are pro-drugs and have comparable activity and tolerability to the parent compounds. Examples of such esters include esters of C_2 to C_5 carboxylic acids, e.g. acetic or propionic acid, benzoic acid, salicylic acid and mandelic acid.

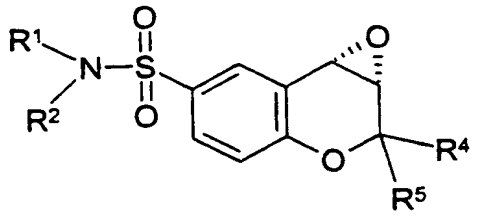
Physiologically acceptable acid addition salts, for example of compounds of formula I, their N-oxides and esters thereof, include salts with inorganic and organic acids, for example salts with hydrochloric, sulphuric, maleic and fumaric acids.

Quaternary ammonium salts, e.g. of compounds of formula I, their N-oxides and esters thereof, include e.g. salts with organo-halides, e.g. alkyl halides. Pharmaceutically acceptable quaternary ammonium salts for use in accordance with the present invention include e.g. such salts with methyl iodide.

Compounds of the invention exist in enantiomeric form, i.e. as optically active antipodes, for example having the [3S, 4R] or [3R, 4S] configuration. The present invention is to be understood as including both the individual enantiomers (e.g. optically active, [3S, 4R] or [3R, 4S], antipodes) as well as mixtures, for example racemic mixtures, thereof. The [3S, 4R] enantiomers are preferred. Suitably, the [3S, 4R] enantiomers are in purified form, i.e. comprising less than 50% enantiomeric contaminants, more suitably in pure or substantially pure form, e.g. comprising less than 10%, preferably 5% or less, e.g. 1 to 2% or less, of [3R, 4S] enantiomers.

Compounds of formula I may be prepared in isolated form

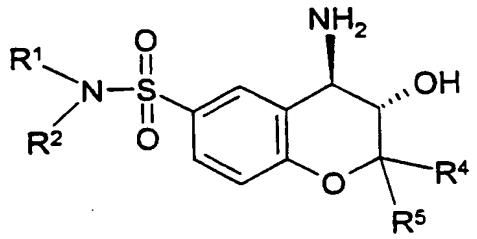
(i) where R^3 in formula I is a group of formula $-N(R^6)-COR^7$ in which R^6 and R^7 together denote 1,3-butadienylene or a group of formula $-(CH_2)_m$ or a group of formula II, by reacting an epoxide of formula



III

where R^1, R^2, R^4 and R^5 are as hereinbefore defined, with a cyclic amide of formula R^7-CO-$N(R^6)H$ such as δ-valerolactam in the presence of a base such as lithium diisopropylamide or lithium hexamethyldisilazide in an aprotic solvent such as N-methylpyrrolidone or tetrahydrofuran or

(ii) where R^3 in formula I is a group of formula $-N(R^6)-COR^7$ in which R^6 is hydrogen and R^7 is a monovalent aromatic or heteroaromatic group, by reacting an amine of formula



IV

where R^1, R^2, R^4 and R^5 are as hereinbefore defined, with an acylating derivative, preferably an acid halide, of a carboxylic acid of formula R^7-COOH where R^7 is as hereinbefore defined, in the presence of a base, or

(iii) for the preparation of a N-oxide or physiologically-hydrolysable and -acceptable ester of a compound of formula I as hereinbefore defined, esterifying the indicated hydroxy group in the compound of formula I to introduce an ester group, for example by reacting a compound of formula I or a N-oxide thereof with an acid halide or anhydride, and/or oxidising a compound of formula I or physiologically-hydrolysable and -acceptable ester thereof as hereinbefore defined; and

recovering the obtained compound of formula I or N-oxide or physiologically-hydrolysable and -acceptable ester thereof in free or in acid addition or quaternary ammonium salt form.

The process step (i) may be carried out using procedures known in the art, for example by reaction at a temperature from ambient to reflux temperature, e.g. as described in Examples 1 and 2 hereinafter.

The process step (ii) may be carried out using procedures known in the art. Thus it may be carried out by reacting an amine of formula IV with an acid anhydride which may be a mixed anhydride, for example of formula R^7-COOCOH, or, preferably, an acid chloride of a carboxylic acid of formula R^7-COOH, such as nicotinoyl chloride. The reaction is suitably carried out at temperatures from 0° to 100°C in an inert solvent such as 1,2-dichloroethane, 1,1,1-trichloroethane or dimethylformamide, in the presence of a base such as an alkali metal carbonate, or trialkylamine, for example as described in Example 3 hereinafter.

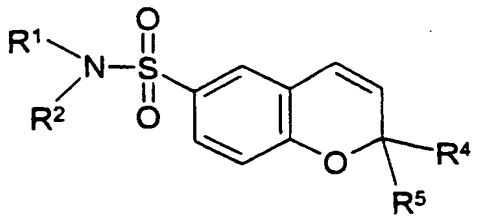
Process step (iii) may be carried out using conventional acylation/N-oxidation procedures. For example, N-oxidation may be carried out by reaction with hydrogen peroxide, m-chloroperbenzoic acid or peracetic acid.

Free bases of formula I may be converted into acid addition salts by reaction with acids or into quaternary ammonium salts by reaction with alkyl halides, e.g. methyl halides, using known procedures. Salts of compounds of formula I may be converted into the free bases by treatment with a base such as an alkali metal hydroxide, carbonate or hydrogencarbonate, using known procedures, or into other salts by treatment with a suitable metal salt of another acid in a medium in which a resultant inorganic salt is insoluble, using known procedures.

Compounds of formula I, their N-oxides and esters in free or salt form may be recovered, i.e isolated from reaction mixtures, using conventional purification procedures.

It will be appreciated that in carrying out the processes hereinbefore described labile groups such as hydroxy groups may be protected, e.g. during acylation procedures by conventional protecting groups.

Epoxides of formula III may be prepared as racemic mixtures by reacting a compound of formula

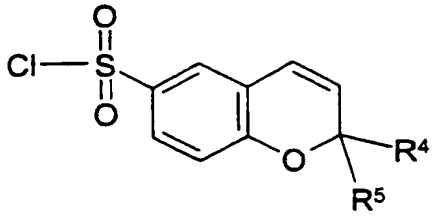


V

where R^1, R^2, R^4 and R^5 are as hereinbefore defined, with N-bromosuccinimide in aqueous dimethyl sulfoxide, followed by reaction with alkali, for example as described hereinafter for the preparation of Intermediate 3b, or by reacting a compound of formula V with 3-chloroperoxybenzoic acid.

Alternatively, epoxides of formula III may be prepared in enantiomerically pure form by stereoselective oxidation of a compound of formula V with a buffered aqueous solution of sodium hypochlorite in the presence of a chiral epoxidation catalyst such as those described in WO91/14694, e.g. (S,S)- or (R,R)-N,N^1-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese (III) chloride as described by Lee, Muci and Jacobsen, Tetrahedron Letters 1991, 32(38), 5055-8, for example as described hereinafter for the preparation of intermediate 3a.

Compounds of formula V may be prepared by reacting a compound of formula



VI

where R^4 and R^5 are as hereinbefore defined with a compound of formula $R^1(R^2)NH$ in the presence of a base such as Hünigs base or triethylamine in an aprotic solvent such as 1,1,1-trichloroethane, for example as described hereinafter for the preparation of Intermediate 2.

Compounds of formula VI may be prepared as described in WO 96/37490, for example as described hereinafter for the preparation of Intermediate 1.

Amines of formula IV may be prepared by reacting an epoxide of formula III with ammonia, suitably in a solvent such as ethanol or isopropanol at a temperature of 60° to 120°C, for example as hereinafter described for the preparation of Intermediate 4.

Compounds of formulae III, IV and V, such as Intermediates 1, 2, 3 and 4 hereinafter described, are novel and form part of the present invention.

Compounds of formula I and their N-oxides, and physiologically-hydrolysable and -acceptable esters thereof, as well as pharmaceutically acceptable acid addition and quaternary ammonium salts of compounds of formula I and said N-oxides and esters, hereinafter referred to collectively as AGENTS OF THE INVENTION, are useful as pharmaceuticals. The compound of Example 1 hereinafter described has a long half-life in the bloodstream and is therefore expected to have a prolonged duration of activity.

AGENTS OF THE INVENTION possess potassium channel opening activity in relation to the plasmalemma membrane as demonstrated by their influence at concentrations in the region of 1 to 500nM on various smooth muscle preparations in accordance with or analogously to the methods described in Quast, Brit.J.Pharma., 91, 569-578 (1987). AGENTS OF THE INVENTION are thereby characterised as K^+ channel opening agents. AGENTS OF THE INVENTION are accordingly useful for the treatment of conditions or disorders for which therapy employing a K^+ channel opening agent is indicated. Therapeutic utility as K^+ channel opening agents may further be demonstrated in standard pharmacological tests, e.g. of cardio-vascular activity, in vitro or in vivo. Thus influence on blood-pressure may be demonstrated in the anaesthetised, cannulated normotensive rat following intra-duodenal administration 1 hr post cannulation. Anti-ischemic activity may be demonstrated in accordance with the methods described in Hof et al., Circ. Res., 62, 679 (1988). AGENTS OF THE INVENTION are accordingly useful, e.g. as smooth muscle relaxants, in particular for use as vasodilating agents, for example for the treatment of hypertension or chronic cardiac insufficiency. They are further useful as anti-ischaemic and anti-vasospastic agents, e.g. for use in the treatment of disturbed blood supply, for example to the heart, skeletal muscle or brain. They are thus useful e.g. for the treatment of angina pectoris, myocardial ischaemia or myocardial infarction; as antifibrillatory agents; for the treatment of disorders of peripheral circulation, e.g. claudicatio intermittens, Morbus Raynaud or venous ulcer; as well as for the treatment, including prophylaxis, of cerebral ischaemia, senile dementia, stroke, subarachnoidal haemorrhage and other related or consequential diseases or discorders.

Activity of compounds of the invention as vasodilating agents may be demonstrated by the following test procedure:

Rhesus monkeys (male, 7.4 -19.4 kg, fasted for 18 hours prior to administration of the compound; supplier: Center for Primatology at the University of Strasbourg) are immobilized with Narketan (ketamine, 10 mg/kg i.m.) and anaesthetized with an infusion of thiopental (8 - 9 mg/kg/h i.v.) via a saphenous vein, using a 20 gauge indwelling cannula (Braunüle) throughout the experiment. Animals are placed in a left lateral position on a heated operating table and allowed to breathe spontaneously. Larynx, epiglottis and pharynx were anaesthetized by topical application of xylocaine spray (10 %, about 10 - 20 mg totally), allowing introduction and placement of a cuffed pediatric endotracheal tube (diameter 4.5 mm). Animals are allowed to rest for 30 minutes prior to baseline blood sampling and data collection.

Systolic and diastolic arterial blood pressure (measured using a pediatric cuff) are monitored by a Siemens Sirecust model 1281. Heart rate and arterial oxygen saturation are measured continuously by pulse oximetry (Pulse Oximeter, Nellcor, Hayward, CA, USA). Body temperature is monitored continuously using a thermistor probe inserted into the oesophagus. Respiratory rate is acquired from measurement of lung function accomplished with a pediatric pulmonary function unit (Sensormedics, Yorba Linda, CA, USA; model 2600), using a pneumotachograph.

The test compound is tested at doses of 0.001, 0.01 and 0.03 mg/kg i.v. It is dissolved in 0.1 ml DMSO and diluted in deionized water (stock solution). Injection solutions are prepared using sterile, pyrogen-free saline 0.9 %, appropriate to an injection volume of 0.1 ml/kg body weight. Injection time via indwelling cannula into the saphenous vein is approximately 30 seconds. Blood samples (2 ml per time-point) are collected from the saphenous vein into EDTA-coated tubes, placed on ice immediately and kept frozen until analysis.

Experiments are performed according to the following time schedule:
- blood sampling and data acquisition in the untreated animal (time 0, baseline)
- administration of test compound
- blood sampling at 5, 15 and 45 minutes after administration
- heart rate and arterial oxygen saturation at 2, 3, 4, 5, 10, 15, 30 and 45 minutes after administration
- arterial blood pressure, respiratory rate and body temperature at 5, 15 and 45 minutes after administration.

Due to high interindividual variation in heart rate and blood pressure, statistical evaluation is done from % change after each treatment compared to baseline levels set as 100 % using the t-test for paired observations of the 'Excel' software package (Microsoft).

AGENTS OF THE INVENTION are also useful as gastro-intestinal, uterine and urinary tract antispastic agents, e.g. for the treatment of irritable bowel disease, diarrhoea, diverticulitis, danger of miscarriage following premature labour and urinary incontinence.

AGENTS OF THE INVENTION are further useful as hair-growth stimulating agents, e.g. for the treatment of hair loss due to ageing, e.g. male alopecia or pattern baldness, or disease-related hair loss for example consequent to infection or disturbance of the immune system, e.g. following cancer chemotherapy or radiation therapy.

Suitable dosages for such uses will of course vary, e.g. depending on the particular condition to be treated, the particular AGENT OF THE INVENTION employed, the mode of administration and the effect desired. In general however, a suitable oral daily dosage, e.g. for anti-hypertensive uses, will be from about 0.03 to about 2.0 mg/kg and for, e.g. anti-ischemic uses, from about 0.015 to about 0.3 mg/kg. For larger mammals, e.g. humans, an indicated oral daily dosage will thus be from about 2 to about 150 mg for anti-hypertensive uses, or from about 1 to about 20 mg for anti-ischemic uses, administered once or in divided doses 2x daily. Oral dosage forms for use in the above indications will thus suitably comprise from about 0.5 or 1.0 to about 20 or 150 mg AGENT OF THE INVENTION together with a pharmaceutically acceptable diluent or carrier therefor.

For use as hair-growth stimulating agents, AGENTS OF THE INVENTION will appropriately be applied topically, e.g. in an appropriate cream, gel or emulsion base or the like as known in the art.

AGENTS OF THE INVENTION possess anti-bronchospastic activity and inhibit or reverse airways hyperreactivity. Moreover, AGENTS OF THE INVENTION do not exhibit cardiovascular side effects, i.e. do not significantly reduce blood pressure, following inhalation at dosages sufficient to inhibit or reverse airways hyperreactivity and relieve or prevent bronchoconstriction. These activities may be demonstrated in pharmacological test models, for example as follows:

REDUCTION OF AIRWAYS HYPERREACTIVITY (AHR)

In the Guinea Pig

The acute injection of pre-formed immune complex renders guinea pigs hyperreactive to histamine. Doses of histamine which cause only a degree of bronchoconstriction prior to administration of immune complex cause a much stronger effect thereafter. Anti-hyperreactive and cardiovascular effects are measured simultaneously to determine a therapeutic window for use of the test compounds in reversal of airways hyperreactivity.

Male Dunkin-Hartley guinea pigs (500-750g) are anaesthetized with sodium phenobarbital (100 mg/kg i.p. Sigma, USA) and sodium pentobarbital (30 mg/kg i.p. Siegfried Handel, CH), then paralyzed with gallamine triethiodide (10 mg/kg i.m. Davis & Greck, USA) and ventilated via a tracheal cannula with a small animal respiratory pump (model KTR 5, Alfos instruments, Biel-Benken, CH) with a mixture of air and oxygen (45:55 v/v, 8 ml/kg, 1 Hz). Airflow is measured at the trachea by a pneumotachograph (Fleisch, type 0000, Zabona, Basel, CH) connected to a differential pressure transducer (model MP45-16-871, Validyne Corp., USA) in line with the respiratory pump. Pressure changes within the thorax are monitored directly via the intrathoracic cannula using a differential pressure transducer (model MP45-24-871 Validyne Corp., USA) so that the pressure difference between the trachea and thorax can be measured and displayed. From these measurements of air flow and transpulmonary pressure, both airway resistance (R_L, cmH2O/(l/s)) and dynamic compliance (C_{dyn}, ml/cmH2O) are calculated after each respiratory cycle with a digital electronic respiratory analyzer (Physiological recorder PR 800, software V.7.2, Mumed Ltd., London, GB). Mean arterial blood pressure and heart rate are recorded from the carotid artery using a pressure transducer. Values for R_L, C_{dyn}, blood pressure and heart rate are displayed continuously on a monitor; data are stored on a 4/33 AST computer.

An allergic reaction is initiated by a 0.3 ml intravenous injection of preformed immune complexes, (prepared by adding 600 µg of bovine gamma globulin in 1 ml of saline to 1.5 ml of guinea pig anti-bovine gamma globulin anti-serum). Intravenous injections of histamine (1.8, 2.4 or 3.2 µg/kg at 10 minute intervals) are used to define the sensitivity of the airways prior to immune complex (IC) exposure. Histamine is injected in a volume of 0.5 ml/kg, bolus, and is immediately flushed in using a Braun infusion pump (Flush = 0.875 ml in 14 sec.). This results in a consistent injection rate for each application of histamine. The dose, which gives an increase in R_L of approximately 100, is then used 30 minutes after IC

exposure and the subsequent histamine doses. Airways hyperreactivity is expressed as a factor:

$$\frac{\text{Post IC increase } R_L \text{ to histamine - Pre IC increase } R_L \text{ to histamine}}{\text{Pre IC increase } R_L \text{ to histamine}}$$

AHR is deemed to have occurred when the factor is larger than 3. The test compound is administered intratracheally after two consistent hyperreactive histamine responses are obtained.

For intratracheal administration, the test compound is dissolved in absolute ethanol. This stock solution has a concentration of 10 mg/ml and is stored at -5 °C. The stock solution is diluted with 0.9% saline to give dosages of 1μg/kg and 10μg/kg in a dose volume of 0.1ml, the solutions for dosing being freshly prepared from stock solution on the day of the experiment.

Data from individual experiments are presented as means ± SEM and unpaired Student's t-test is used for comparison between treatments at individual time points. Significance is assumed at the 5% probability level using the 'Excel' V.5.0 software package (Microsoft). ED_{50} and ED_{20} values, representing the doses which give a 50% reduction of airways hyperreactivity and a 20% reduction of mean arterial blood pressure, respectively, are determined graphically.

The compound of Example 1, administered at a dose of 1 μg/kg, causes a maximum inhibition of AHR of 45% at 15 minutes after dosing, while at a dose of 10 μg/kg it causes an inhibition of AHR of 45% at 15 minutes after dosing and a maximum inhibition of 74% at 30 minutes after dosing. The ED_{50} value for the compound of Example 1 is 4 μg/kg. At dosages of 1 μg/kg and 10 μg/kg, the compound of Example 1 causes no significant change in mean arterial blood pressure, and no significant effect on heart rate; the ED_{20} value, determined graphically using the results for the 1 μg/kg and 10 μg/kg doses and the results of a further experiment at a dose of 100 μg/kg, is 25 μg/kg.

BRONCHORELAXATION

AGENTS OF THE INVENTION are tested in cryopreserved human bronchi. Small bronchi are mounted in organ baths (isometric recording under a resting tension of 1g). The bronchi generate spontaneous tone. Concentration-response curves are determined by cumulative additions of test compound, each compound being added when the maximum effect has been produced by the previous concentration. Papaverine (300 μM) is added at the end of the concentration response curves to induce complete relaxation of the preparation, and this effect as taken as 100% relaxation.

AGENTS OF THE INVENTION are accordingly useful in particular as agents for the therapy of airways hyperreactivity e.g. as agents for the symptomatic as well as prophylactic treatment of obstructive or inflammatory airways disease, in particular asthma. By continued administration, AGENTS OF THE INVENTION may be used for the control, restriction or reversal of airways hyperreactivity (for example, exercise-induced asthma or nocturnal asthma) or to provide advance protection against recurrence of bronchoconstrictor attack consequential to obstructive or inflammatory airways disease, in particular asthma. The words "treatment" and "treating" as used throughout the present specification and claims in relation to use of AGENTS OF THE INVENTION for the treatment of obstructive or inflammatory airways disease, in particular asthma, are accordingly to be understood as embracing both prophylactic as well as symptomatic (i.e. bronchodilator) modes of therapy, unless otherwise specified.

In accordance with the foregoing the present invention also provides:

A method for the treatment of any disease or condition herein specified; in particular

a. A method for the treatment of obstructive or inflammatory airways disease; including

a.1. A method for the symptomatic treatment of inflammatory or obstructive airways disease; or

a.2. A method for the prophylactic treatment of inflammatory or obstructive airways disease, e.g. for the treatment of airways hyperreactivity; or

b. A method for the treatment of hypertension, chronic cardiac insufficiency or ischaemia; or

c. A method for the treatment of urinary incontinence;

- in a subject, particularly a human subject, in need thereof, which method comprises administering to said subject an effective amount of an AGENT OF THE INVENTION;

or, in the alternative:

An AGENT OF THE INVENTION for use as a pharmaceutical, e.g. for use in the treatment of any disease or condition as herein specified, in particular for use in the treatment of obstructive or inflammatory airways disease, e.g. as indicated under a.1, a.2, b or c above; or

A pharmaceutical composition comprising an AGENT OF THE INVENTION, or use of an AGENT OF THE INVENTION in the preparation of a pharmaceutical composition, for use in the treatment of any disease or condition herein specified, in particular for use in the treatment of obstructive or inflammatory airways disease, e.g. as indicated under a.1, a.2, b or c above.

Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and, especially, extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now more correctly identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory (e.g. β_2 adrenergic) therapy. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning

dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Inflammatory or obstructive airways diseases to which the present invention is applicable also include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis. Further inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), and bronchitis, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy, e.g. β-agonist bronchodilator therapy, including in particular usage of AGENTS OF THE INVENTION as bronchodilators for the treatment of chronic or acute airways obstruction as well as dyspnea, associated with any of the said diseases or conditions.

For use in the treatment of inflammatory or obstructive airways disease, AGENTS OF THE INVENTION may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions. Preferably however they will be administered by the pulmonary route, e.g. by inhalation from an appropriate nebulizer, inhaler or like device as known in the art.

Dosages employed in the treatment of inflammatory or obstructive airways disease will of course vary depending, e.g. on the particular condition to be treated, the particular AGENT OF THE INVENTION employed, the mode of administration and the effect desired. Appropriate dosages of the AGENTS OF THE INVENTION for administration by inhalation, e.g. for suppression of airways hyperreactivity in the course of asthma therapy in humans, will thus be anticipated to be about the same as or somewhat higher than those conventionally required using salbutamol. In general, for pulmonary administration for larger mammals, e.g. humans, a suitable daily dosage delivered to the lungs will be of the order of from about 1μg to about 1000μg, in particular from about 10μg to about 500μg, suitably administered from an inhaler device with administration effected once or from 2 to

4x daily, in a series of from 1 to 4 puffs at each administration. For oral administration a suitable daily dosage will generally be of the order of from about 0.1 to about 30μg/kg. A suitable oral daily dosage for larger mammals, e.g. humans, will thus be of the order of from about 7μg to about 2.1mg for a 70 kg individual, administered in a single dose, in divided doses administered from 2 to 4x daily, or in sustained release form. Oral unit dosage forms for such use will thus suitably comprise from about 1.75μg to about 2.1mg AGENT OF THE INVENTION together with a pharmaceutically acceptable diluent or carrier therefor.

In accordance with the foregoing the present invention also provides a pharmaceutical composition comprising an AGENT OF THE INVENTION optionally together with a pharmaceutically acceptable diluent or carrier therefor, e.g., in inhalable form. Such compositions may be manufactured in conventional manner, e.g. for pulmonary administration by compounding AGENT OF THE INVENTION in finely divided disperse particulate form, e.g. together with finely divided lactose as a carrier/diluent to form an inhalable powder. AGENTS OF THE INVENTION in a form suitable for pulmonary administration may be administered using a suitable inhaler device, e.g., a metered dose inhaler, so that the invention additionally includes an inhaler device, e.g., a metered dose inhaler, containing AGENT OF THE INVENTION in inhalable form.

The invention is illustrated by the following Examples. Intermediates used in the Examples, and intermediates used in the preparation of those intermediates are prepared as follows:

Intermediate 1

2,2-dimethyl-2H-1-benzopyran-6-sulphonyl chloride

A solution of n-butyl lithium in hexane (20 mL of 1.6 M, 32 mmol) is added to a stirred solution of 6-bromo-2,2-dimethyl-2H-1-benzopyran (7.17 g, 30 mmol) in dry tetrahydrofuran (100 mL) at -78°C under an argon atmosphere. The mixture is stirred for 1 hour at -78°C and then a stream of sulphur dioxide gas is bubbled through the solution for 30 minutes, after which the resulting mixture is allowed to warm to 20°C. The mixture is then evaporated to dryness under reduced pressure to give a residue which is suspended in dry hexane (300 mL), cooled to 0°C and treated dropwise with a solution of sulphuryl chloride (2.53 mL, 4.21 g, 31 mmol) in dry hexane (30 mL). The resulting mixture is stirred for 30 minutes at 0°C, followed by 60 minutes at 20°C and then evaporated to dryness under reduced pressure to afford the title compound as a pink crystalline solid.

Intermediate 2

(2a) 2,2-dimethyl-2H-1-benzopyran-6-sulphonamide

A solution of ammonia in 2-propanol (125 mL of 2 M) is added to a stirred suspension of 2,2-dimethyl-2H-1-benzopyran-6-sulphonyl chloride (25.87 g, 100 mmol) in chloroform (200 mL) and stirred at 20°C for 16 hours. The solvent and excess reagents are evaporated off under reduced pressure to yield the crude product. This is purified by column chromatography on silica gel, eluent 10% acetone in cyclohexane, and recrystallised from tert-butyl methyl ether to give the title compound as a colourless crystalline solid, m.p. 139-141°C and having the following physical characteristics:
1H-NMR (δ-$CDCl_3$): 1.46 (s, 6H), 4.75 (broad s, 2H), 5.71 (d, J = 9.9 Hz, 1H), 6.32 (d, J = 9.9 Hz, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H) and 7.65 (dd, J = 2.3, 8.5 Hz, 1H).

The following compound is prepared analogously by utilising N-(2,2-dimethylpropyl)-N-methylamine in place of ammonia:
(2b) 2,2-dimethyl-N-(2,2-dimethylpropyl)-N-methyl-2H-1-benzopyran-6-sulphonamide m.p. 152-153 °C and having the following physical characteristics:
1H-NMR (δ-DMSO-d6): 0.91 (s, 9H), 1.40 (s, 6H), 2.68 (s, 3H), 2.75 (s, 2H), 5.86 (d, J = 9.9 Hz, 1H), 6.55 (d, J = 9.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 2.3, 8.4 Hz, 1H) and 7.52 (d, J = 2.3 Hz, 1H).

Intermediate 3a

(3S,4S)-1a,7b-Dihydro-2,2-dimethyl-2H-oxireno[c][1]benzopyran-6-sulphonamide.

A mixture of aqueous sodium hypochlorite (20 mL of 14%) and aqueous sodium phosphate, dibasic (40 mL of 0.5 M) is added dropwise, over 1 hour to a stirred mixture of 2,2-dimethyl-2H-1-benzopyran-6-sulphonamide (2.4 g, 10 mmol) and (S,S)-(+)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (0.4 g, 0.73 mmol) in isopropyl acetate (40 mL) at 20°C. The mixture is stirred for an additional 4 hours, filtered and extracted with ethyl acetate (2 x 500 mL). The combined extracts are dried (Na2SO4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product

which is purified by chromatography on silica gel, eluent 10 - 50% ethyl acetate in hexane, to give the title compound as a yellow oil.

Intermediate 3b

1a,7b-Dihydro-2,2-dimethyl-*N*-(2,2-dimethylpropyl)-*N*-methyl-2H-oxireno[c][1]benzopyran-6-sulphonamide.

N-Bromosuccinimide (3.82 g, 21.4 mmol) is added to a stirred solution of 2,2-dimethyl-*N*-methyl-*N*-(2,2-dimethylpropyl)-2H-1-benzopyran-6-sulphonamide (6.46 g, 20 mmol) in dimethylsulphoxide (50 mL) and water (0.94 g, 0.52 mmol) at 15°C. The mixture is stirred for 30 minutes and then treated with a solution of sodium hydroxide (4.0 g, 100 mmol) in dioxan-water (100 mL of 50%) and stirred at 20°C for 30 minutes. The mixture is concentrated to 25% volume by evaporation under reduced pressure, treated with saturated aqueous ammonium chloride solution (300 mL) and extracted with ethyl acetate (2 x 200 mL). The combined exracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography (silica gel, 10% acetone in hexane) and recrystallised from hexane to give the title compound as a pale-brown crystalline solid, having the following physical characteristics:
^{1}H-NMR (δ-$CDCl_3$): 1.01 (s, 9H), 1.30 (s, 3H), 1.56 (s, 3H), 1.61 (s, 3H), 2.80 (s, 2H), 3.56 (d, J = 5.5 Hz, 1H), 3.97 (d, J = 5.5 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 7.66 (dd, J = 2.3, 9.0 Hz, 1H) and 7.81 (d, J = 2.3 Hz, 1H).

Intermediate 4

N-(2,2-Dimethylpropyl)-*N*-methyl-(4-amino-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran)-6-sulphonamide.

1a,7b-Dihydro-2,2-dimethyl-*N*-(2,2-dimethylpropyl)-*N*-methyl-2H-oxireno[c][1]benzopyran-6-sulphonamide (4.00 g, 11.8 mmol) is treated with a saturated solution of ammonia in ethanol (60 mL) and heated at 80°C in an autoclave for 18 hours. The solvent is evaporated off under reduced pressure to yield the crude product which is purified by chromatography on silica gel, eluent 25% aqueous NH_3-CH_3OH-tert-butyl methyl ether (1:5:94) and recrystallised from tetrahydrofuran – hexane to give the title compound as colourless crystalline solid, having the following physical characteristics:

^{1}H-NMR (δ-$CDCl_3$): 1.01 (s, 9H), 1.25 (s, 3H), 1.54 (s, 3H), 1.85 (broad s, 3H), 2.80 (s, 2H), 3.35 (d, J = 9 Hz, 1H), 3.68 (d, J = 9 Hz), 6.87 (d, J = 8.6 Hz, 1H), 7.55 (dd, J = 2.3, 8.6 Hz, 1H) and 7.83 (d, J = 2.3 Hz, 1H).

Example 1

3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-sulphonamide.

A stirred solution of anhydrous 2-piperidinone (1.61 g, 16.25 mmol) in dry tetrahydrofuran (80 mL) at 0°C under an argon atmosphere is treated with a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (16.3 mL of 1.0M, 16.3 mmol) and stirred at 20°C for 2 hours. The resulting suspension is treated with a solution of (3*S*,4*S*)-1a,7b-Dihydro-2,2-dimethyl-2H-oxireno[c][1]benzopyran-6-sulphonamide (Intermediate 3a; 0.83 g, 3.25 mmol) in dry tetrahydrofuran (50 mL) and heated at 85°C for 17 hours. The mixture is cooled to 15°C, treated with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with ethyl actetate (2 x 80 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography (silica gel, eluent 3% CH_3OH-CH_2Cl_2) to give the title compound as a colourless crystalline solid, m.p. 198-201°C, having the following physical characteristics:
^{1}H-NMR (δ-$CDCl_3$): 1.08 (s, 3H), 1.37 (s, 3H), 1.55-1.76 (m, 4H), 2.38 (m, 2H), 2.65-3.00 (m, 2H), 3.61 (d, J = 10.2 Hz, 1H), 5.09 (broad s, 2H), 5.14 (s, 1H), 5.75 (d, J = 10.2 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H) and 7.55 (dd, J = 2.3, 8.6 Hz, 1H).

Example 2

N-(2,2-Dimethylpropyl)-*N*-methyl-[3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-sulphonamide.

A stirred solution of anhydrous 2-piperidinone (1.00 g, 10 mmol) in dry tetrahydrofuran (50 mL) at 0°C under an argon atmosphere is treated with a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (10 mL of 1.0M, 10 mmol) and stirred at 20°C for 2 hours. The resulting suspension is treated with a solution of 1a,7b-dihydro-2,2-dimethyl-*N*-(2,2-dimethylpropyl)-*N*-methyl-2H-oxireno[c][1]benzopyran-6-sulphonamide (Intermediate 3b; 1.69 g, 5 mmol) in dry tetrahydrofuran (30 mL) and heated at 80°C for 20 hours. The

mixture is cooled to 15°C, treated with a saturated aqueous solution of ammonium chloride (100 mL) and extracted with ethyl actetate (2 x 80 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography (silica gel, eluent 5% ethanol-toluene and recrystallised from tetrahydrofuran-hexane to give the title compound as a colourless crystalline solid, m.p. 221-223°C.

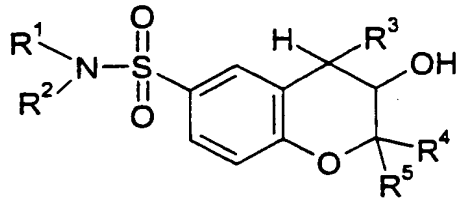
Example 3

trans-*N*-[3,4-Dihydro-2,2-dimethyl-6-[(*N*-methyl-2,2-dimethylpropylamino)sulphonyl]-3-hydroxy-2*H*-1-benzopyran-4-yl]-3-pyridinecarboxamide.

A stirred solution of *N*-(2,2-dimethylpropyl)-*N*-methyl-(4-amino-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1-benzopyran)-6-sulphonamide (Intermediate 4; 1.96 g, 5.5 mmol), triethylamine (1.70 mL, 1.23 g, 12 mmol), 4-dimethylaminopyridine (0.17 g, 1.4 mmol) and dry dimethylformamide (15 mL) in 1,1,1-trichloroethane (35 mL) under an argon atmosphere, is treated with nicotinoyl chloride hydrochloride (1.08 g, 5.9 mmol) and stirred at 18°C for 4 hours. The solvent is evaporated off under reduced pressure to give a residue which is treated with saturated aqueous ammonium chloride solution (100 mL) and extracted with ethyl acetate (2 x 80 mL). The combined exracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography (silica gel, eluent 25% aqueous NH_3-CH_3OH-tert-butyl methyl ether (1:5:94) and recrystallised from tetrahydrofuran-hexane to give the title compound as a colourless crystalline solid, m.p. 222-224°C.

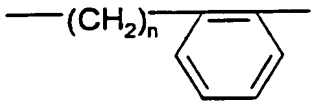
Claims

1. A compound of formula



I

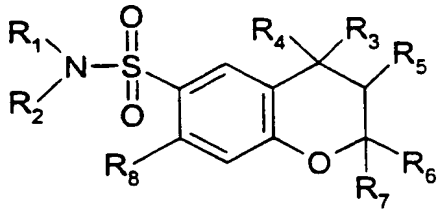
where the indicated OH group in the 3- position is in the trans position with respect to R^3, and R^1 and R^2 are independently hydrogen or C_1 to C_5 alkyl, R^3 is a group of formula $-N(R^6)-COR^7$ where R^6 is hydrogen or C_1 to C_5 alkyl and R^7 is a C_6 to C_{10} monovalent aromatic group or a monovalent heteroaromatic group having a 5- or 6- membered heteraromatic ring, or R^6 and R^7 together are 1,3-butadienylene or denote a group of formula $-(CH_2)_m-$ or



II

in which m is an integer of from 3 to 5 and n is 1 or 2, and R^4 and R^5 are, independently, C_1 to C_5 alkyl; or a N-oxide thereof; or a physiologically-hydrolysable and -acceptable ester of a compound of formula I or N-oxide thereof; or a physiologically acceptable acid addition or quaternary ammonium salt of a compound of formula I, or of an ester or N-oxide thereof.

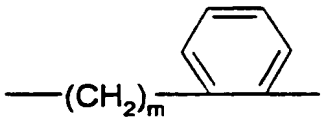
2. A compound according to claim 1 other than when present as a metabolite following administration to a subject of a compound of formula A :



A

wherein R_1 is phenyl, R_2 is hydrogen, R_3 is a group of formula $-N(R_9)-COR_{10}$ in which R_9 and R_{10} together denote $-(CH_2)_4-$, R_4 is hydrogen, R_5 is hydroxy in the trans position with respect to R_3, R_6 and R_7 are each methyl and R_8 is hydrogen.

3. A compound according to claim 1 other than when present as a metabolite following administration to a subject of a compound of formula A wherein R_1 is aryl, R_2 is H or C_{1-5}alkyl, or is C_{2-5}alkylene linked to R_1, R_3 is a group of formula $-N(R_9)-COR_{10}$ wherein R_9 is hydrogen and R_{10} is phenyl or pyridyl, or R_9 and R_{10} together are 1,3-butadienylene or represent a group of formula $-(CH_2)_n-$ or



in which n is an integer of from 3 to 5 inclusive and m is 1 or 2, R_4 is hydrogen and R_5 is hydroxy in the trans position with respect to R_3, R_6 and R_7 are independently C_1-C_5-alkyl, and R_8 is hydrogen or C_1-C_5-alkyl; or N-oxide thereof; or physiologically-hydrolysable and -acceptable ester of such a compound or N-oxide, or acid addition or quarternary ammonium salt of such a compound, N-oxide or ester.

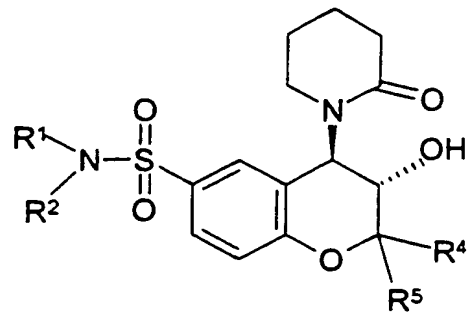
4. A compound according to claim 1, 2 or 3, in which R^1 and R^2 are each hydrogen or R^1 is methyl and R^2 is 2,2-dimethylpropyl.

5. A compound according to claim 1, 2 or 3, in which R^6 in a group of formula $-N(R^6)-COR^7$ is hydrogen.

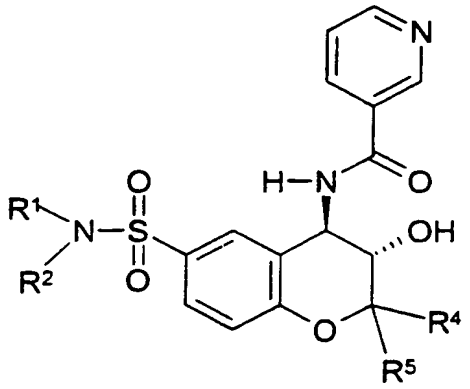
6. A compound according to any one of claims 1 to 5, in which R^7 as an aromatic or heteroaromatic group is phenyl, optionally substituted by 1 to 3 substituents selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, halogen-substituted C_1-C_5 alkyl or halogen, naphthyl or hetreoaryl containing nitrogen in the ring.

7. A compound according to any one of claims 1 to 6, in which R^3 is a group of formula $-N(R^6)-COR^7$ in which R^6 is hydrogen and R^7 is pyridyl, or R^6 and R^7 together are 1,3-butadienylene, trimethylene or tetramethylene.

8. A compound according to any one of claims 1 to 4 which is of formula IA or IB



IA



IB

where R^1, R^2, R^4 and R^5 are as defined in claim 1 or 4.

9. A compound according to claim 8, in which R^1 and R^2 are each hydrogen, or R^1 is methyl and R^2 is 2,2-dimethylpropyl; and R^4 and R^5 are each methyl.

10. A compound according to claim 8 which is of formula 1A in which R^1 and R^2 are each hydrogen and R^4 and R^5 are each methyl.

11. A compound according to any one of claims 1 and 4 to 10 in isolated form.

12. A compound according to any one of claims 1 and 4 to 10 for use as a pharmaceutical.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 and 4 to 10 together with a phramaceutically acceptable diluent or carrier therefor.

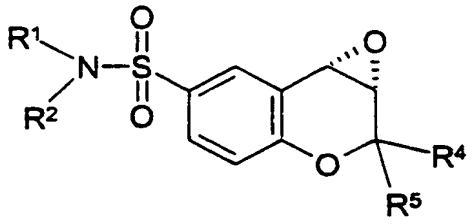
14. A pharmaceutical composition comprising a compound according to any one of claims 1 and 4 to 10 for use in the treatment of an obstructive or inflammatory airways disease, hypertension, chronic cardiac insufficiency, ischaemia or urinary incontinence.

15. Use of a compound according to any one of claims 1 and 4 to 10 in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease, hypertension, chronic cardiac insufficiency, ischaemia or urinary incontinence.

16. A method of treating an obstructive or inflammatory airways disease, hypertension, chronic cardiac insufficiency, ischaemia or urinary incontinence in a subject in need thereof, which comprises administering to said subject an effective amount of compound according to any one of claims 1 and 4 to 10.

17. A method of preparing a compound according to claim 1, which comprises

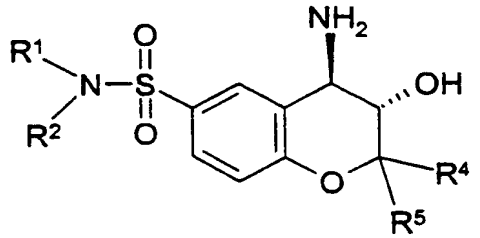
(i) where R^3 in formula I is a group of formula $-N(R^6)-COR^7$ in which R^6 and R^7 together denote 1,3-butadienylene or a group of formula $-(CH_2)_m$ or a group of formula II, reacting an epoxide of formula



III

where R^1, R^2, R^4 and R^5 are as defined in claim 1, with a cyclic amide of formula R^7-CO-$N(R^6)H$ in the presence of a base such as lithium diisopropylamide or lithium hexamethyldisilazide in an aprotic solvent or

(ii) where R^3 in formula I is a group of formula $-N(R^6)-COR^7$ in which R^6 is hydrogen and R^7 is a monovalent aromatic or heteroaromatic group, reacting an amine of formula



IV

where R^1, R^2, R^4 and R^5 are as defined in claim 1, with an acylating derivative, preferably an acid halide, of a carboxylic acid of formula R^7-COOH where R^7 is as defined in claim 1, in the presence of a base, or

(iii) for the preparation of a N-oxide or physiologically-hydrolysable and -acceptable ester of a compound of formula I, esterifying the indicated hydroxy group in the compound of formula I to introduce an ester group, and/or oxidising a compound of formula I or physiologically-hydrolysable and -acceptable ester thereof; and

recovering the obtained compound of formula I or N-oxide or physiologically-hydrolysable and -acceptable ester thereof in free or in acid addition or quaternary ammonium salt form.

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 99/07539

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D407/12 C07D407/04 A61K31/35 A61K31/44 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 339 562 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 2 November 1989 (1989-11-02) claims 1-6	1-17
Y	WO 96 37490 A (SANDOZ-PATENT-GMBH) 28 November 1996 (1996-11-28) cited in the application claims 1-8	1-17
Y	EP 0 366 273 A (BEECHAM GROUP PLC) 2 May 1990 (1990-05-02) claims 1-10	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 1999	28/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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Intern al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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